American Journal of Medical Genetics 63:492–500 (1996)

Sex Ratios in Fetuses and Liveborn Infants With Autosomal Aneuploidy

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Ten data sources were used substantially to increase the available data for estimating fetal and livebirth sex ratios for Patau (trisomy 13), Edwards (trisomy 18), and Down (trisomy 21) syndromes and controls. The fetal sex ratio estimate was 0.88 (N = 584) for trisomy 13, 0.90 (N = 1702) for trisomy 18, and 1.16 (N = 3154) for trisomy 21. All were significantly different from prenatal controls (1.07). The estimated ratios in prenatal controls were 1.28 (N = 1409) for CVSs and 1.06 (N = 49427) for amniocenteses, indicating a clear differential selection against males, mostly during the first half of fetal development. By contrast, there were no sex ratio differences for any of the trisomies when comparing gestational ages <16 and >16 weeks. The livebirth sex ratio estimate was 0.90 (N = 293) for trisomy 13, 0.63 (N = 497) for trisomy 18, and 1.15 (N = 6424) for trisomy 21, the latter two being statistically different than controls (1.05) (N = 3660707). These ratios for trisomies 13 and 18 were also statistically different than the ratio for trisomy 21. Only in trisomy 18 did the sex ratios in fetuses and livebirths differ, indicating a prenatal selection against males >16 weeks. No effects of maternal age or race were found on these estimates for any of the fetal or livebirth trisomies. Sex ratios for translocations and mosaics were also estimated for these aneuploids. Compared to previous estimates, these results are less extreme, most likely because of larger sample sizes and less sample bias. They support the hypothesis that these trisomy sex ratios are skewed at conception, or become so during embryonic development through differential intrauterine selection. The estimate for Down syndrome livebirths is also consistent with the hypothesis that its higher sex ratio is associated with paternal nondisjunction.

KEY WORDS: fetal sex ratios, livebirth sex ratios, autosomal aneuploids, Patau syndrome, Edwards Syndrome, Down syndrome

INTRODUCTION

The chromosomal basis of Down syndrome as trisomy 21 was first described in 1959; in the following year, the Edwards and Patau syndromes were ascribed to trisomy 18 and 13, respectively. These three trisomies are the only autosomal aneuploids occurring with appreciable frequency in livebirths, currently estimated at 1/920 for Down syndrome [Krivchenia et al., 1993], 1/9,270 for Edwards syndrome, and 1/21,600 for Patau syndrome [Hecht and Hecht, 1987]. Hassold and Jacobs [1984] reported an incidence in clinically recognized pregnancies of 1/225 for trisomy 21 and ~1/550 for both trisomies 18 and 13. These substantial changes in frequency between fetal development and livebirths indicate strong selection pressure against these aneuploids during the prenatal period. Studies to date have not determined whether this selection pressure acts differentially on males and females.

Sex ratios are defined as the number of males divided by the number of females (sometimes multiplied by 100). The primary sex ratio is that found at conception,

Received for publication October 2, 1995.

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and the secondary ratio is that found at birth. Extrapolations suggest the primary ratio for all conceptions of whites may be ~1.15 [Huether, 1990]. Among livebirths, Khoury et al. [1984] calculated the sex ratio to be 1.06 for ~14 million whites in the United States. The major factor affecting the well-documented secondary sex ratio appears to be race, with a low of 1.02 in American Indians [Khoury et al., 1984] to 1.15 reported in Korea [Kang and Cho, 1962].

Estimates of sex ratios in the three autosomal aneuploids—where available—have varied widely among published studies. Most have focused on livebirths with Down syndrome, but because of bias of ascertainment, much of the early data needs to be dismissed [Huether, 1990]. However, even among nine studies judged to be unbiased through high ascertainment of karyotyped livebirths, reported sex ratios for Down syndrome have varied from a low of 0.90 (N = 162) [Mikkelsen et al., 1976], to a high of 1.35 (N = 290) [Mikkelsen, 1985]. Four published studies reporting the sex ratio of livebirths for Edwards syndrome all indicated a preponderance of females, with a range of 0.26 (N = 143) [Taylor, 1968] to 0.43 (N = 76) [Goldstein and Nielsen, 1988], whereas among four studies on Patau syndrome, the range was from 0.87 (N = 178) [Magenis et al., 1968] to 1.38 (N = 19) [Goldstein and Nielsen, 1988]. These data likely provide the basis for statements such as Hecht and Hecht [1987] ". . . (I)t is known that females with trisomy 18 and perhaps trisomy 13 tend more often to survive to birth than males. . . ."

Equally few estimates are available for these aneuploids in fetuses diagnosed prenatally, often with small sample sizes, which results in greater variation than in livebirths. However, even sex ratios of control fetuses have varied widely among published studies, from 0.71 (N = 370) [Eiben et al., 1990] to 1.32 (N = 443) [Hassold et al., 1983], where both were based upon spontaneous abortion data.

These widely disparate findings both within and among these aneuploids may be the result of sampling error, biases resulting from the manner of data collection, the different populations sampled (e.g., cases through prenatal diagnosis versus spontaneous abortion), an early prenatal selection acting differentially on the sexes, or they may represent true biologic differences (differences associated with etiology). Given the increasing availability of creditable data, this study was undertaken in an attempt to clarify some of these issues and to determine if these findings could indirectly contribute to understanding whether different etiologic mechanisms exist for these aneuploids.

The specific objectives of this study were: (1) to determine the overall sex ratios in fetuses and livebirths for each of the three autosomal aneuploids and controls and statistically to test for homogeneity among them, (2) to determine whether differential selection between the sexes is occurring during the prenatal period for each aneuploid and controls, (3) to compare sex ratios within each syndrome by chromosomal type (trisomy, translocation, or mosaic), and (4) to determine whether the variables of gestational age, maternal age, and race affect these sex ratios.

MATERIALS AND METHODS

Table I summarizes the sources for all data utilized in the study, including time periods and the number of individual cases (or controls) obtained from each source. Data on livebirths for the three syndromes were either collected by University of Cincinnati staff or directly obtained from a total of 16 cytogenetic laboratories, two birth defect monitoring programs, and for Down syndrome, Ohio birth certificates through the Division of Data Services (corrected for false positives using hospital medical records and cytogenetic laboratory records). Ascertainment from the monitoring programs is considered to be essentially complete, so that sex biases due to incomplete ascertainment are believed nonexistent in these data. However, potential biases exist from the cytogenetic laboratories and the Ohio birth certificates in that these data sources do not have complete ascertainment of all livebirth cases within a population. Data on control livebirths were obtained from Ohio and California birth certificates.

Data on fetal cases prenatally diagnosed through chromosome analysis were obtained from five cytogenetic laboratories and the Genetic Diseases Branch of the California Health Authority, which collects cytogenetic data statewide. Additionally, data on fetuses prenatally diagnosed with Down syndrome were collected from 13 cytogenetic laboratories in Ohio. No biases are known to exist in these data sets as all successful karyotypes were ascertained. Data for control fetuses were obtained from three cytogenetic laboratories (Table I). Where available, data on chromosome type (trisomy, translocation, or mosaic), maternal age, race, and gestational age were obtained along with each individual's sex for all livebirths and fetuses. Sex was determined by karyotype for all cases, except for some livebirths from birth defect monitoring programs and Ohio birth certificates. These determinations came from active abstraction of hospital medical records.

Data were analyzed using either 2 × r heterogeneity Chi-square tests or a multiple logistic regression model. Chi-square analysis was used to compare the sex ratios of single categorical variables such as maternal age within each trisomy. Logistic regression was used to test for differences among populations contributing to each single categorical variable (e.g., testing homogeneity of maternal age distributions among six populations).

RESULTS

Table II provides the number of cases and sex ratios found for all prenatal and livebirth aneuploids by chromosome type, as well as control data, for all races. The small difference between prenatal (1.07) and livebirth (1.05) sex ratios in the controls was not statistically different ($P > 0.1$), although there is a slight reduction in male livebirths. As shown later (Table III), the sex ratio in prenatal controls depends heavily upon the proportional representation of chorionic villus sampling (CVS) and amniocentesis in the data set. These data provide an estimate of the sex ratio for prenatal controls based upon a much larger sample size than has been previously available.

TABLE I. Populations and Facilities From Which Data Were Obtained by Years, Information Available, and Number of Cases for All Races

		No. of cases							
		Prenatally diagnosed				Livebirths			
		Syndrome				Syndrome			
Database	Years	Patau	Edwards	Down	Control	Patau	Edwards	Down	Control
Southwest Ohio[b, d, e]	1970–89							748	
Metropolitan Atlanta Congenital Defects Program[b, d, e]	1970–89					47	68	566	
California Birth Defects Monitoring Program[a, b, d, e]	1983–91					192	321	2,226	880,393
Ohio, rest of[a, b, c, d]	1970–93	26	93	266	22,423	21	27	2,273	2,780,314
Emory Cytogenetics Lab[a, b, c, d]	1977–95	19	52	119	17,980	10	16	165	
Integrated Genetics[a, b, c]	1984–95	194	528	1,504		44	74	808	
California Genetics Disease Branch[a, b, c, d]	1989–94	373	899	1,166					
Atlanta[a, b, c, d]	1976–92	36	53	128					
Genetics Institute[b, c]	1987–90	39	130		429				
British Columbia[b, c, d]	1973–89			93	10,004				
Totals		687	1,755	3,276	50,836	314	506	6,786	3,660,707

[a] Karyotypes available.
[b] Maternal age available.
[c] Gestational age available.
[d] Race available.
[e] Completely ascertained data sets.

TABLE II. Overall Sex Ratios of Fetuses and Livebirths by Aneuploid and Chromosomal Type (and Controls) for All Races

	Patau syndrome		Edwards syndrome		Down syndrome		Controls	
	N	Ratio	N	Ratio	N	Ratio	N	Ratio
Controls[a]								
Prenatal							50,836	1.07
Livebirth							3,660,707	1.05
Trisomy[b]								
Prenatal[c]	584	0.88	1,702	0.90	3,154	1.16		
Livebirth								
Complete[d]	239	0.88	389	0.69	3,345	1.10		
Others[e]	54	1.00	108	0.42	3,079	1.21		
Mosaic								
Prenatal[c]	44	0.76	41	0.52	79	0.61		
Livebirth								
Complete[d]					70	1.41		
Others[e]	2	—	6	0.50	50	0.92		
Translocation								
Prenatal[c]	59	1.11	12	1.40	43	1.53		
Livebirth								
Complete[d]					125	1.35		
Others[e]	19	1.11	3	—	117	1.13		

[a] Cases completely ascertained (California Birth Defects, Monitoring Program, rest of OH, Emory Cytogenetics Lab, BC, Genetics Institute databases).
[b] Excludes mosaic and translocation cases where karyotypes were available.
[c] All prenatally diagnosed cases (California Genetics Disease Branch, BC, Integrated Genetics, Genetics Institute databases).
[d] Complete ascertainment of livebirth cases (Metropolitan Atlanta Congenital Defects Program, California Birth Defects Monitoring Program, SW OH databases).
[e] Livebirth cases where ascertainment was not complete (rest of OH, Emory Cytogenetics Lab, Integrated Genetics databases).

TABLE III. Sex Ratios of Fetuses by Gestational Age for Each Trisomy (Excludes Known Mosaics andTranslocations) and Controls for All Races

Gestational age	Patau syndrome		Edwards syndrome		Down syndrome		Controls[a]	
	N	Ratio	N	Ratio	N	Ratio	N	Ratio
<16	139	0.72	380	0.90	620	1.18	1,409	1.28*
≥16	416	0.94	1,252	0.91	2,245	1.14	49,427	1.06*
Unknowns	29	0.93	70	0.94	289	1.28		
Totals	584	0.88	1,702	0.90	3,154	1.16	50,836	1.07

[a] Control data subdivisions are by cvs and amniocentesis, respectively.
* Significantly different ($P < 0.01$).

For each of the comparisons below where data were obtained from more than one source, the various data sets within each aneuploid were first statistically compared for homogeneity. In all cases no statistical differences were found ($P > 0.05$). Thus the data sets were combined and are presented in the various tables. In those instances of small sample sizes, e.g., translocations and mosaics, the data were collated without testing for differences among data sets within each aneuploid.

Prenatal Sex Ratio Comparisons

Data on the fetal trisomy cases came from six different cytogenetic sources (Table I). The trisomy prenatal sex ratio for each syndrome (Table II) was compared to prenatal controls (1.07); trisomy 13 (0.88) and 18 (0.90) were significantly lower ($P < 0.05$, $P < 0.01$, respectively), and trisomy 21 (1.16) significantly higher ($P < 0.05$). Three significant differences were found when translocation and mosaic prenatal sex ratios were compared to their respective trisomy ratios and to prenatal controls. The mosaic Down syndrome ratio (0.61) was significantly lower than the trisomy 21 (1.16) and control (1.07) sex ratios (both $P < 0.05$), and the mosaic Edwards syndrome ratio (0.52) was significantly lower than the control ($P < 0.05$). However, small sample sizes in the other translocation and mosaic comparisons may limit the ability to detect statistical differences. Interestingly, all three mosaic data sets have sex ratios much lower than controls, whereas all three translocation data sets have sex ratios greater than controls.

Livebirth Sex Ratio Comparisons

As shown in Table II, a distinction was made for a number of livebirth comparisons as to whether the data were completely ascertained within a population; those that were not are listed as "others" and could contain biases of ascertainment. Comparisons were made for each of the five livebirth categories where both types of data were available. A statistical difference was found

only for trisomy 18, where the sex ratio from data not completely ascertained (0.42) was lower than that having complete ascertainment (0.69) ($P < 0.05$). This lower value for incomplete ascertainment is consistent with estimates from the literature and suggests an ascertainment bias favoring female cases in these studies. For the other comparisons where no differences were found between levels of ascertainment, the data sets were combined for further analyses.

These combined livebirth data sets for trisomies 13 and 21, and the completely ascertained data set for trisomy 18, were compared to livebirth controls and to each other. Both the livebirth sex ratios for trisomies 18 (0.69) and 21 (1.15) were significantly different than livebirth controls (1.05) (both $P < 0.01$), whereas the livebirth sex ratio for trisomy 13 (0.90) was not different from controls. Compared to each other, trisomy 13 (0.90) and 18 (0.69) had statistically similar sex ratios, but both were different from trisomy 21 (1.15) (both $P < 0.05$). For Down syndrome, the sex ratios of the combined livebirth data for translocations (1.24) and mosaics (1.18) were each compared to trisomy 21 (1.15) and livebirth controls (1.05), and no statistical differences were found (all $P > 0.1$) (Patau and Edwards syndrome had too few data for a meaningful comparison here).

Prenatal vs. Livebirth Sex Ratio Comparisons

Comparisons were made between prenatal and livebirth sex ratios within each aneuploid for trisomies; only trisomy 18 showed a statistical difference between the prenatals (0.90) and livebirths (0.69) ($P < 0.05$). This indicates that biologic selection against males is occurring between prenatal diagnosis and birth for fetuses with trisomy 18. By contrast, there is excellent agreement between prenatal and livebirth sex ratios for trisomy 13 (0.88 and 0.90, respectively), and trisomy 21 (1.16 and 1.15, respectively), indicating no differential sexual selection occurring for these two trisomies during this time period. Additional comparisons for Down syndrome were made between sex ratios in translocation prenatals (1.53) and livebirths (1.24), which were not statistically different, and mosaic prenatals (0.61) and livebirths (1.21) ($P < 0.05$), which showed prenatals were significantly lower. Here, the indication is that biologic selection against females is occurring between prenatal diagnosis and birth for fetuses with mosaic Down syndrome.

Effect of Gestational Age in Trisomy and Control Fetuses

Table III shows the fetal sex ratios by two gestational age categories for each trisomy (excludes known mosaics and translocations) and controls. Controls were classified by procedure, either CVS or amniocentesis, rather than by the specific gestational age categories. Still, the data are generally comparable in that the great majority of control amniocenteses were $\geq$16 weeks gestation given the dates of their collection (Table I). For the same reason, most of the aneuploids <16 weeks were CVSs.

Statistical comparisons between gestational ages show no differences for any of the three aneuploids, while there is clear statistical difference for controls (1.28 vs. 1.06) ($P < 0.01$). The control ratios indicate a definite biologic selection against males occurring between the two gestational categories for "normal" fetuses. Additionally, since the amniocentesis value of 1.06 is consistent with the livebirth control value of 1.05, most biologic selection must be occurring prior to 16 weeks of gestation. The same selection against males is occurring for trisomy 18 (Table II), but it is *after* the time of amniocentesis rather than before, as the two gestational ages are essentially identical. A similar trend of selection against males during gestation may be indicated in fetuses with Down syndrome (1.18–1.14–1.10 for livebirth populations completely ascertained), but it is not as pronounced. No such selection appears to be operating at any time during gestation for trisomy 13.

Effect of Maternal Age in Fetuses and Livebirths

Table IV shows the fetal and livebirth sex ratios by six maternal age categories for each trisomy (excludes known mosaics and translocations) and controls. All 10 data sources shown in Table I were able to supply maternal ages for some if not all of their data sets, but some mothers' ages were not available within data sets. For fetuses, none of the trisomies, or either of the control data sets (CVS and amniocentesis) showed any effect of maternal age on the sex ratios. Not even trends are evident among any of the data sets, including control amniocenteses, where a data set of almost 50,000 individuals minimizes the effects of sampling. Similarly, each of the four livebirth data sets shows homogeneity among the maternal age categories (all χ^2 values $P > 0.25$). Again, no trends are visible for any of the trisomies; in the controls there is a slight reduction in sex ratio among older women. The data in Table IV clearly indicate maternal age is not having a meaningful effect on the sex ratio of either prenatally diagnosed fetuses or livebirths for any of the trisomies or controls.

Effect of Race in Fetuses and Livebirths

Table V shows the fetal and livebirth sex ratios by four race categories for each trisomy (excludes known mosaics and translocations) and livebirth controls. Of the 10 data sources, eight were able to supply race information for at least some of their data sets. For each trisomy and controls, race was available for at least half of the fetuses and three fourths of the livebirths. For fetuses, all of the trisomy and control sex ratios are in good statistical agreement among the racial categories. Whereas the individual race values vary a good deal within some of the trisomies, this variation can be attributed to small sample sizes. For livebirths, the sex ratios are also in good agreement among the race categories for the three trisomies, with no trends being visible for any of the trisomies. By contrast, the livebirth control sex ratios show a highly significant difference among the race categories even though the range is only from 1.03 for blacks to 1.07 for others. These control data are consistent with previously reported studies indicating racial differences among sex ratios in livebirths. However, the data in Table V indicate that for the trisomies and fetal controls, race is not having a meaningful effect on the sex ratio.

TABLE IV. Sex Ratios of Fetuses and Livebirths by Maternal Age Quinquennia for Each Trisomy (Excludes Known Mosaics and Translocations) and Controls for All Races

	Fetuses									
	Syndrome						Controls			
Maternal	Patau		Edwards		Down		CVS		Amniocentesis	
age	N	Ratio	N	Ratio	N	Ratio	N	Ratio	N	Ratio
<20	21	1.10	38	0.81	37	1.06	6	1.00	766	1.02
20–24	40	0.82	116	1.47	79	0.72	21	1.63	1,883	1.05
25–29	59	1.11	214	1.02	153	0.96	63	0.85	3,694	1.05
30–34	95	1.21	262	1.03	453	1.25	154	1.37	7,657	1.00
35–39	191	0.66	551	0.81	1,481	1.18	906	1.24	30,211	1.08
≤40	136	0.89	453	0.84	899	1.17	289	1.43	5,167	1.07
Totals	542	0.87	1,634	0.92	3,102	1.16	1,439	1.27	49,378	1.06

	Livebirths							
	Syndrome							
Maternal	Patau		Edwards		Down		Controls	
age	N	Ratio	N	Ratio	N	Ratio	N	Ratio
<20	18	1.00	29	0.93	532	1.03	565,658	1.05
20–24	51	0.89	73	0.46	1,086	1.14	1,139,226	1.05
25–29	71	0.87	86	0.76	1,330	1.18	1,076,705	1.05
30–34	61	1.03	99	0.65	1,195	1.14	615,947	1.05
35–39[a]	47	0.96	106	0.66	840	1.18	234,108	1.04
≤40	—	—	—	—	526	1.16	29,063	1.04
Totals	248	0.94	393	0.65	5,509	1.15	3,660,707	1.05

[a] Category is ≥35 for Patau and Edwards syndromes.

DISCUSSION

The major objective of this study was to estimate sex ratios for the three autosomal aneuploids in both fetuses and livebirths using the better quality data increasingly available. Given the 10 data sources used (Table I), we have been able to increase substantially the published data for obtaining these estimates in both aneuploids and prenatal controls. A major advantage of these larger sample sizes is that they help reduce the effect of sampling variation, one likely cause of the considerable differences in estimates previously available. A second likely cause, sampling bias, particularly in livebirths, has also been effectively eliminated by using some completely ascertained data sets.

Prenatal Comparisons and Gestational Age Effects

For prenatal controls, more recent studies (since 1980) estimating sex ratios have utilized three different types of data: (1) conceptuses spontaneously aborted, (2) conceptuses electively terminated, and (3) conceptuses undergoing diagnosis for chromosome abnormalities (our approach). Most studies have used (1), but only spontaneous abortions that were chromosomally normal. Even where maternal contamination is stated not to be an issue, there are conflicting results. Hassold et al. [1983] found a sex ratio of 1.32 (N = 443), Byrne and Warburton [1987] found 1.30 (N = 529), and Jakobovits [1991] found 1.36 (N = 251) (although no karyotype analyses were carried out), whereas Eiben et al. [1990] found 0.71 (N = 370) and Bartels et al. [1990] found 0.77 (N = 250). In contrast to these inconsistencies in spontaneous abortions, studies of electively terminated fetuses have typically found an excess of males present. Kellokumpu-Lehtinen and Pelliniemi [1984] found a sex ratio of 1.17 (N = 551) in mostly first trimester abortions, and Jakobovits et al. [1986] found 1.09 (N = 749) in second trimester abortions. In the only two studies we found estimating sex ratios in (all) pregnancies monitored for chromosome abnormalities (both using only CVS), Mikkelsen and Ayme [1987] found a sex ratio of 1.16 (N = 335) and Bartels et al. [1990] found 1.17 (N = 396).

Our prenatal control results are supportive of all of these studies with the exception of those finding an excess of females in spontaneous abortions. An excess of males in spontaneous abortions is consistent with our findings of a sex ratio reduction from 1.28 in CVS to 1.06 in amniocenteses. These values are also similar to those found in the first and second trimester elective terminations and to the two other CVS studies, even though our CVS ratio is somewhat higher. Adding our results to these studies clearly indicates there is an excess of males in early conceptuses, and that by birth, this sex ratio is significantly reduced through differential selection against males, mostly during the first half of fetal development.

Only trisomy 18 appears to exhibit this substantial loss of males during the fetal period (0.90 to 0.69, Table II), although the selection is during the second half of fetal development. Changes in the sex ratio for trisomy 21 show slight selection against males during the prenatal period observed.

TABLE V. Sex Ratios of Fetuses and Livebirths by Race for Each Trisomy (Excludes Known Mosaics and Translocations) and Controls

	Fetuses							
	Syndrome							
	Patau		Edwards		Down		Controls	
Race	N	Ratio	N	Ratio	N	Ratio	N	Ratio
Whites	238	0.83	635	0.90	903	1.13	31,875	1.06
Blacks	18	1.00	34	0.70	56	0.93	—	—
Hispanics	50	0.92	147	1.26	223	1.17	—	—
Others	40	1.22	140	0.73	143	0.96	4,418	1.06
Totals	346	0.89	956	0.91	1,325	1.11	36,293	1.06

	Livebirths							
	Syndrome							
	Patau		Edwards		Down		Controls	
Race	N	Ratio	N	Ratio	N	Ratio	N	Ratio
Whites	116	0.81	179	0.69	4,049	1.18	2,269,531	1.06
Blacks	16	0.78	32	1.29	603	1.15	930,112	1.03
Hispanics	57	0.84	97	0.67	486	1.05	362,470	1.04
Others	49	0.96	82	0.52	381	1.03	94,358	1.07
Totals	238	0.84	390	0.68	5,519	1.15	3,656,471	1.05

For each of the trisomies, however, their overall prenatal sex ratios were significantly different from prenatal controls: trisomies 13 (0.88) and 18 (0.91) being below, and trisomy 21 (1.16) above the controls (1.07). Summarizing data for trisomy 13 fetuses from three studies [Hassold et al., 1983; Jacobs et al., 1987; Fujinaga et al., 1990], all based upon spontaneous abortions, yielded a sex ratio of 1.20 (N = 101). Two studies [Goldstein and Nielsen, 1988; Snijders et al., 1994], estimating the sex ratio through prenatal diagnosis, had a sex ratio of 0.69 (N = 27). For trisomy 18 fetuses, only the spontaneous abortion study by Hassold et al. [1983] included data for trisomy 18 (sex ratio of 1.50, N = 35). The two prenatal diagnosis studies found a ratio of 0.97 (N = 69), similar to ours (0.90). The different means of obtaining the data most likely explain the different results for both trisomies. These combined data sets from the literature are small compared to our prenatal sample sizes of 584 for trisomy 13 and 1,702 for trisomy 18, but other than the spontaneous abortion data, are consistent with it. They reinforce the conclusion that the skewed sex distributions for trisomies 13 and 18 are clearly present by the time of CVS.

The prenatal data available in the literature for trisomy 21 are somewhat greater. Eight studies obtained data on prenatally diagnosed fetuses [Mikkelsen, 1981; Nielsen et al., 1981; Pilgaard and Mikkelsen, 1985; Iselius and Lindsten, 1986; Mikkelsen and Ayme, 1987; Staples et al., 1991; Mikkelsen, 1992; Snijders et al., 1994]. The combined sex ratio from these studies is 1.18 (N = 683). By contrast [Hassold et al., 1983] found a sex ratio of 1.67 (N = 80) in spontaneous abortions, again emphasizing the consistent difference between these two means of data collection for all three trisomies. Our results found a sex ratio of 1.16 (N = 3154), very similar to that of the eight studies collectively.

Only one of the above control studies on spontaneous abortions [Eiben et al., 1990] included data on maternal ages and found no difference among three mater-nal age categories. Only one study on the prenatal trisomies (Down syndrome) included maternal age [Snijders et al., 1994], finding a sex ratio of 1.11 (N = 40) for women 35–39 years of age, and 1.85 (N = 37) for women ≥40. The former value is similar to ours of 1.18 (N = 1481) for those 35–39, but the latter differs substantially from 1.17 (N = 899) for women ≥40 years of age. The small sample sizes in Snijders' study could account for such differences. Thus our data showing no effect of maternal age on the sex ratios of trisomy or control fetuses are generally consistent with the small amount of data available in the literature.

Livebirth Comparisons and Effects of Maternal Age and Race

For livebirth controls, there is a very extensive literature discussing sex ratio estimates and the numerous variables that may affect it. Most of this is not relevant to the present context, except that it is known sex ratios differ among races (by ~10% maximum), and that if maternal age has an effect on sex ratios, it is not large [James, 1987]. The values presented in Tables IV and V for livebirth controls by maternal age and race are essentially identical to those found in the literature.

The livebirth sex ratios for trisomies 18 (0.69) and 21 (1.15) were statistically different from livebirth controls (1.05) and each other, and trisomy 13 (0.90) was different from trisomy 21 (Table II). For trisomy 13, four studies [Magenis et al., 1968; Taylor, 1968; Goldstein and Nielsen, 1988; Baty et al., 1994] estimate the livebirth sex ratio, and when combined yield a value of 0.92 (N = 256), essentially identical to our estimate. Combining our data with that from the literature gives

a value of 0.91 (N = 549), still showing no statistical difference with livebirth controls ($P > 0.10$).

For trisomy 18, four studies [Taylor, 1968; Le Marec and Senecal, 1975; Goldstein and Nielsen, 1988; Baty et al., 1994] yield a combined sex ratio estimate of 0.32 (N = 580). This value is substantially lower than our estimate from complete livebirth data sets of 0.69 (Table II) but is consistent with the estimate from our incomplete data sets of 0.42. Weber [1967] and Baty et al. [1994] indicate that there is a substantially lower differential survival of males beginning at birth for both trisomies 13 and 18 and thus suggest the livebirth sex ratio estimates for each trisomy are likely biased downward based upon the incomplete ascertainment of the data sets. Our results support this view, given the (statistically) different estimates of our complete versus incomplete data sets for trisomy 18. Thus it seems likely that the true sex ratio for trisomy 18 livebirths is closer to the value of 0.69 and that the other estimates are low because of sampling bias.

For trisomy 21 livebirths, the completely ascertained data sets produced a sex ratio estimate of 1.10, whereas populations incompletely ascertained produced an estimate of 1.21 (Table II). These were not statistically different and were therefore combined for a value of 1.15. This was statistically higher than the 1.05 in livebirth controls, although the estimate from complete data sets alone did not differ from controls ($P > 0.20$). These data are at some variance with the generally accepted view that the sex ratio of livebirths with Down syndrome is substantially skewed toward an excess of males. However, a detailed review of livebirth sex ratio estimates in 32 populations over the last 30 years by Huether [1990] revealed that only 11 of these provided unbiased estimates of sex ratios in his opinion. Of these, two were statistically higher than controls, three were suggestive of an excess of males (>1.20), and six hovered around the controls (0.90–1.14). Two additional publications in the 1990s with completely ascertained populations both showed sex ratio estimates statistically higher than controls [Staples et al., 1991; Mikkelsen, 1992]. For livebirths with Down syndrome, the average sex ratio from these 14 unbiased studies (including our complete data sets) is 1.18 (N = 10223). In our opinion, this should be viewed as the best estimate available and includes mosaics and translocations as well as trisomies. Although still indicating an excess of males, this value is substantially lower than in many of the earlier estimates.

For translocation livebirths (Table II), the data in our study as well as the literature for Patau and Edwards syndromes is insufficient for further comment. However, for Down syndrome, Huether [1990] reviewed eight studies, finding two with high ascertainment and a high percentage of chromosome analysis. Combining the two studies gives a sex ratio of 1.12 (N = 119). Staples et al. [1991] found a ratio of 0.35 (N = 23). Both of these values are below our estimate of 1.35 (N = 125) from the highly ascertained data sets, although the numbers involved are relatively small. Combining all three data sets yields an estimate of 1.12 (N = 267), not dissimilar to livebirth controls, trisomy 21s, or overall Down syndrome.

Our data showed no significant effect of maternal age on the sex ratios of fetuses or livebirths for any of the syndromes or controls (Table IV). Two highly ascertained studies on Down syndrome [Iselius and Lindsten, 1986; Staples et al., 1991] are supportive of this conclusion, although both suggest a higher ratio among older women.

Conclusions and Relationship to Etiology of Aneuploids

Combining the data presented here with appropriate literature studies provides for a few relatively firm conclusions. The strong differential selection pressure against males occurring in prenatal controls during the first half of fetal development is not occurring in any of the three aneuploids. However, for trisomy 18, there is a significant selection pressure against males between the time of amniocentesis and birth. The opposite selection—against females—appears to be occurring only in mosaic Down syndrome. Perhaps more importantly, there is a significant excess of females in fetuses for trisomy 13 and in both fetuses and livebirths in trisomy 18, whereas in Down syndrome there is a significant excess of males in both fetuses and livebirths, although none of these values is as extreme as suggested by previous studies. Gestational age, maternal age, or race do not appear to be having significant effects on these sex ratios in either fetuses or livebirths.

Do these data aid, either directly or indirectly, in our understanding of the etiologic basis for any of these aneuploids? Hug [1951] thought so, although his data led him to believe there was a much higher sex ratio for Down syndrome than proposed here and that there was a strong inverse correlation between maternal age and sex ratio. He concluded the primary sex ratio (at conception) is at least 2.00 for Down syndrome and that this had etiologic consequences. Hassold et al. [1984] also believed that the increased ratio occurs at conception. Our data are supportive of this idea for all three trisomies in that the prenatal data for each is significantly different than prenatal controls and that the aberrant livebirth sex ratios are already established in fetuses <16 weeks of gestational age (Table III). However, early differential intrauterine selection cannot be ruled out as a basis for these data.

Hassold et al. [1984] specifically proposed that the increased sex ratio for Down syndrome is associated with paternal nondisjunction where the extra 21st chromosome preferentially segregates with the Y chromosome. Several studies in the 1980s tried to obtain data relative to this hypothesis, but their parental origin data were based upon cytogenetic heteromorphisms rather than molecular analysis. Petersen et al. [1993] provide data based upon DNA polymorphisms and found strongly supportive evidence. They found a sex ratio of 3.5 (N = 27) in those cases where the extra 21st chromosome was paternally derived through a meiotic nondisjunction. They also observed a high sex ratio for both meiosis I and II errors and suggest mechanisms that might explain these results.

Considering the recent molecular evidence that indicates only ~5% of Down syndrome nondisjunctions are paternally derived [Antonarakis, 1993] and assuming a sex ratio of 1.06 for all maternally derived cases, a sex ratio of 3.5 is *exactly* that needed in paternally derived cases to reach an overall sex ratio of 1.18. This was stated earlier to be the current best estimate available for livebirths with Down syndrome. The lack of any maternal age effect for either fetuses or livebirths in our data (Table IV) is also evidence in support of the higher sex ratio being paternally derived in Down syndrome. Further, to the degree this hypothesis is correct relative to trisomy 21, it suggests different mechanisms are involved in trisomy 13 and 18 nondisjunctions, as their sex ratios were found to be significantly below that of trisomy 21. This study also demonstrates that having good epidemiologic data (and resulting estimates) is an important correlate to these recent molecular studies on sex ratios.

ACKNOWLEDGMENTS

We acknowledge Dr. Tina Milatovich and Mr. Larry Edmonds for contributing data, Ms. Zahava Berkowitz for contributing and collating data, and Ms. Marylin Raybaud for her help in data collation and analysis.

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